at

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

UNITED STATES FOOD AND DRUG ADMINISTRATION

ICH PUBLIC MEETING

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Introductory Remarks

MS. SHOWALTER: We are going to go ahead and get started. My name is Janet Showalter. I am the ICH Coordinator for FDA. We have a number of presentations to go through for you. This is a preparation meeting for the Brussels meeting. It is something we do prior to every ICH meeting as a matter of transparency and also to let you know exactly what we are planning to do once we get there so that we can get your input so that can use that as we negotiate in Brussels.

The session is being recorded. There is going to be a transcript available. I believe that will be made available on the website following the meeting. Again, since there are not very many of us here this morning, I would like us to be informal. I think you are invited to ask questions as we go or you can hold them until the end for the presentations.

One of the things that we do prior to starting this every time, and this may be old-hat for a lot of you, we do like to go through and give a brief overview of ICH and the process, what it is all about.

This morning Christelle Anquez of my staff in the Office of International Programs is going to provide that presentation so I think we will try to sort of zip through some things so that we make sure we get to your questions.

Christelle?

ICH General Overview

MS. ANQUEZ: Good morning, everyone. I will get started and then you will have the slides on the screen. I will go rapidly because I am sure you are very familiar with ICH and this is very basic.

So ICH stands for International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use. It is a unique approach. It comes from the agreement between the European Union, Japan and the USA to take action on Harmonization. It is a joint initiative involving regulators and industry as equal partners in technical discussions.

ICH Guidelines are developed to harmonize the technology requirements that must be met for regulatory submissions in the EU, Japan and U.S. ICH was created in 1990 at a meeting hosted by the European Federation of Pharmaceutical Industries

and Associations located in Brussels. Representatives from industry and regulatory authorities met to plan for the ICH conference. At the beginning, it was just to be one conference and it led to thirteen years of work. It also established the terms of reference and the method of working.

The ICH objectives are the identification and elimination of the need to duplicate studies, to meet different regulatory requirements. This leads to a more efficient use of resources, human, animal, material, in the R&D process as a consequence. The bottom line is quicker access to patients of safe and effective new medicines.

Since the focus of ICH has been on the ICH has been on the technical requirements for medicinal products containing new drugs and because the majority of these new drugs and medicines are developed in the Western European Union, in Western Europe, Japan and the U.S., when ICH was established, it was agreed that its scope would be confined to registration in these three regions.

These are the six founding members of ICH. EU was this European Commission, EMEA; EFPIA, the Ministry of Health, Labor and Welfare, Japanese

Pharmaceutical Manufacturers Association, the FDA and PhRMA.

ICH is administered by the ICH Steering Committee which is supported by the ICH Secretariat. IFPMA is located in Geneva and provides the Secretariat to participate as a non-party member of this joint committee. The second part of ICH is the technical part where the science and technology occurs within the expert working group.

On the steering committee, there are two members per party and a coordinator is the IFPMA, which is a non-voting member, and three observers, one for Canada, EFTA--the European Free Trade Area--and WHO. The role of the steering committee is to oversee and monitor the Harmonization process.

The ICH topics are divided into four categories; safety that relates to preclinical studies. Efficacy relates to clinical studies. Quality and the last category is regulatory communications. That include MedDRA and other electronic items.

The guidances are posted for each region and, for the U.S., it is posted on the CDER and

CBER website. The steering committee has outlined the ICH for monitoring the process of harmonization work. Step 1 is the expert working group are building scientific consensus. The draft document, when it is agreed upon, it goes to the steering committee. The steering committee approves it by signing off on it and then it is released on the three regions for publication and comments.

The comments are brought back by the regulatory authorities to the working group. They are discussed. The draft is revised if necessary, agreed upon and then, if the steering committee agrees with it, it is signed off. The regulators sign off on it. The last step, Step 5, the document, the guidance, is implemented in the three regions.

ICH also organizes a final conference to present the work done for open and public discussion. The first conference was in Brussels in 1991. The second conference was in Orlando in 1993. The third conference was in Yokohama in 1995, then in Brussels in 1997. The fifth one was in San Diego in 2000 when the CTD got signed off. The sixth conference to come will be in Osaka in 2003.

Thank you.

MS. SHOWALTER: Thank you, Christelle.

I am going to do the next presentation on the agenda which is one of the big items of discussion for the upcoming Brussels meeting is going to be the GMP Program for the 21st Century.

GMPs

MS. SHOWALTER: The way we are going to do the meeting today, we are going to go through some of the big topics for the Brussels meeting. One of the big items on the agenda is actually the ICH portion of the GMP Program, the Drug Product Quality, or GMP, Program for the 21st Century.

What I want to do today is give you some idea of the work that we have done to prepare for this meeting and give you an idea of the kinds of things that we are going to be talking about in Brussels.

First of all, I want to let you know the people that are on this committee, this is the International Working Group for the GMP Initiative. It probably helps to put this in context a little if you understand that that there are more than fourteen groups. I say more than fourteen because it grows kind of by leaps and bounds all time and I

think several have been added.

When we started this, there were fourteen working groups. The international group is one of those fourteen. This just gives you some idea of the magnitude of the initiative because you look at the long list of names that are participating in the international section. On all of the various committees, there is a list equally as long and, in fact, some people are participating on more than one.

So I think it gives you some idea of the priority and the extent to which this is going to make a huge change in FDA.

When we decided to take the GMP Initiative up in ICH, we had some concerns about whether ICH would be an appropriate venue for this. As we went, we reflected on some of the kinds of topics that we had taken in the past to ICH and we realized that there were some similarities with other topics in terms of the process that we might use for this one.

So we are doing kind of a "lessons learned" from what we have done with gene therapy and also with pharmacovigilance. The process we used for those was to really get a discussion going

of the technical experts that we had already within the ICH framework and then pull in some opportunities for outside expertise as well, and to also make sure that, before we embarked upon a single topic, that we really had a good understanding of the lay of the land in the area.

So I really want to give you concept today that we are not really jumping very smartly on this but we are taking our time to stop and reflect and deliberate so that we can end up with a good and timely product.

Another topic that we also reflected on was the work that we had done with a previous GMP topic and that was on the Q7A topic, GMPs for APIs. We though there would also be a number of lessons learned from this as well. In fact, we were looking at this topic because this is one where we had a great deal of success in accommodating our domestic time line even while making some serious steps forward internationally.

The way that we did this, we realized, was to have a concrete idea of exactly what we wanted to do and then start marching down a very well-specified pathway.

So, in working with my GMP international

group, what we set out to do was to identify two major areas where we thought we would play an important role. The desired outcome or the goal for this initiative was firstly to have harmonized international scientific standards. This would be done under the auspices of ICH.

When we looked at this topic, we really set our sites on standards for drug-product quality or GMPs that would promote technological innovation. Then we realized that that would not exactly get the entire job done but there would also need to be an additional goal. This was a more long-term plan for international regulatory cooperation and the end product for that would actually be an FDA concept paper that would outline the long-term plan for regulatory collaboration.

This has actually a much longer time line associated with it. That FDA concept paper will probably not be ready for another, I would say, eighteen months or so or at the moment when we actually revisit the GMP initiative.

So, in getting ready for this talk today, one of the things that I wanted to do, and I want to go through these fairly quickly, was to give you an idea of the buildup and how we are getting to

this point, this sort of critical moment in time that we are going to come to at the Brussels meeting.

As you can see from the next few slides that I put together, the international working group has actually met a about once a month. We have had some very good discussions, a lot of very important exchange, not with just the folks at CDER but also with our colleagues in vet medicine, in Biologics and ORA and the Office of Regulatory Affairs.

We started this process in August of last year. We had our first meeting. That is when we realized we would need to do an ICH concept paper, that we would need to have Janet Woodcock actually address the steering committee in September of that year at the Washington ICH meeting.

Following that, we did some additional brain storming in September after the meeting and realized that the first track would be a short-term deliverable. Basically, what we were told at the ICH meeting in Washington was that, if we wanted this topic to go forward in ICH, we would need to have something to our ICH partners by the end of November. I can tell you, this was no easy task

trying to get a single concept paper that everybody across many centers and ORA could agree on.

But we did meet our time line. Then we had some additional meetings to talk about what kind of document might accompany the concept paper. The concept paper is actually something that ICH requires before it takes up a topic. We realize that it was pretty sketchy at best in terms of what we knew last August or last September in trying to put this together.

We realized, at our October meeting on October 22, the need to put together what we call a white paper. The white paper actually is something that lays out the lay of the land, the current situation in FDA and what we wanted to get out of the overall GMP initiative and how this would relate to ICH.

Then we had a number of other meetings at the same time that we were proceeding down this track of doing the concept paper, the white paper and so forth. Also, the agency was trying to move forward with a number of contracts and getting those finalized.

At the early stage of that, we thought that there could be an international component to

those contracts but, as time wore on, we realized that probably wouldn't pan out. So our task became sort of in the fall through the winter to put together the white paper, to get that reviewed and vetted within the agency.

You will see we had meetings in November, more meetings on that in December, culminating in a February finalization of the white paper and also this dovetailed very nicely--some of you may have attended the April GMP workshop here in Washington. One of the things that we were trying to do is to get all of this great load of information that the various working groups have and figure out how we can coalesce that into sort of a unified program.

This did come together at the April workshop. We heard a lot about what the international component of the GMP programs should be. There were many, many references to harmonization. This made us very happy the fact that we had early on decided to, at a minimum, take this to ICH and, perhaps, later on to other venues.

One of the other venues that you will find repeatedly gets mentioned, and we had a discussion of this at our February meeting, is the PIC/s. That is something that we are currently

investigating as a venue for further regulatory collaboration on this topic.

We had additional meetings in March of this year. We also, at that point, got an update from our folks in FDA that we are working on the contract process. This is when the international component was actually deleted. However, there is still interest in soliciting some information from other countries. Some of those that we have set our sites upon for various reasons are Japan, because we work closely with them and they are a market leader in the pharmaceutical area. Also, there seems to be some potential for lessons learned with Switzerland, Canada and Australia. We understand that Australia has recently made some changes to more or less align themselves with the PIC/s scheme.

There have been some additional meetings and discussion in May. At this point, we were finalizing our action plan and I believe that the long-term deliverable of investigating other venues was also approved by the GMP steering committee.

So now, as we are really sort of on the brink of Brussels meeting, what we have been doing is meeting with the international working group and

also with team that is going to ICH to negotiate this topic. We have really refined our thinking a lot since when we embarked upon this last August. I think it is worth noting that some of the topics that repeatedly come up as contenders for some sort of harmonization are things like general definitions for risk and quality, process capability, pharmaceutical development and also variations and changes.

One of the things that also we set our sites on in June was the fact that an overall goal for this workshop should be development of a strategic plan. One of the reasons for this, I think, is also, as part of our lessons learned and the process of some level of introspection is that most of you have followed ICH know that we developed a series of guidelines for the drug-review pharmaceutical-development phase.

Then, at the end, we kind of realized, well, gee, there is an opportunity for the CTD now because we have all these guidelines. This is a case where we are trying to do it the other way, something that ICH hasn't exactly done in the past, and really put together the strategic plan and what all the various pieces are. So we are starting

broadly and then we will, from that process, figure out which of those discrete topic areas we may want to take up, and kind of the rationale for why we take them up when we do.

Again, ICH has not done this kind of planning and so I think this will be a useful experiment to see how this shapes up at the Brussels meeting.

I just want to go back very briefly to give you some idea about the concept paper. I think all of this is in line with talk that Christelle previously gave on the procedures. One thing we just make sure we take note of is that the scope of the concept paper, which I do think is critical because we may be going forward to other venues for some of other aspects, we were very precise there and defined the scope, which was to assess the current state of and future directions for assuring drug-product quality.

This really had to do with things that could promote or encourage innovation as sort of our reason for being NICH.

Just a few words about the white paper. It was drafted by Brian Hasselbalch at FDA. We went through a very elaborate process of

organizational vetting to make sure that it really did represent the agency's best thinking. One of the things that you will also notice is that our goal here was to have all of the ICH partners come into the Brussels meeting with sort of the same amount of information so that that could be basically a level playing field.

If you attended the April workshop, you would have noticed that EFPIA did put forward their paper already. They presented that in April. In addition to that, we understand that we are going to be getting a paper, which is the European white paper, perhaps sometime this week or next, that they are about to finish theirs. I know the Japanese are working on something very similar as well.

So the goal would be to start the workshop with some fundamental background from all of the sponsors which would be shared and used as the basis for those discussions.

The time line, just to go over for you the time line for ICH, again, starting with that Brussels meeting, really, that will be a two-day discussion meeting talking about the current state of play and the identification of potential topics.

It is very unlikely that there could be a expert working meeting. Probably that will not happen until Spring of 2004. I think it is likelier that we will have some level of additional discussion at the meeting not in Tokyo but in Osaka in November just prior to ICH-6. I think probably that will be a concept-paper drafting session.

So when you look at the extended time line, you will notice that we are really not talking about having any sort of the Step-2 document until, at the earliest, the Fall of 2004. It probably won't happen then. It probably will actually be maybe in the Spring of 2005 or sometime that year, depending on how many extra meetings they might want to have and how many would be agreeable to the steering committee to fund.

Back to the April GMP workshop summary and the international implications of that workshop, just to give you some idea of the kinds of things, again, that were mentioned that would have some sort of international component, I think. You see that we are sort of coalescing repeatedly along the same topic lines, but these would be things like how do you assess process capability, what are the general principles to assess new measuring

technologies, again general principles for different new manufacturing technologies, general principles about a quality-system approach. Always, we end up talking about risk assessment and risk management.

The other thing that repeatedly comes up internationally and also it is important here at FDA is how we link the review side with the inspection side. We are spending a great deal of time trying to work that out and what that means in terms of an overall quality-system approach.

The Brussels meeting, the snapshot; again, it is a two-day meeting. It will be co-chaired by the EU and by FDA. Those chairs are Gordon Monroe and Ajaz Hussain from FDA, Monroe for Europe. Again, what we are really trying to do is keep the discussion fairly broad, on the broad themes that are important for developing the strategic plan.

There will be a report to the steering committee that probably will come up on Friday morning. The meeting, itself, probably will start Wednesday afternoon and go all day Thursday. I think it is very likely, and this is just a forecast, but we are hoping that maybe two to three ICH topics could be selected. These would be the

things we would write the concept papers for in the fall.

Also, it is important to note that it is very likely at this meeting that pharmaceutical development will be agreed as an ICH topic. That is being folded under the GMP drug-product quality umbrella. It probably will also go down a very specific and discrete quality pathway within the ICH framework since there already was a lot of consensus about taking this up as a topic previously.

Again, just to reiterate, and I don't think there are any surprises here is you get used to seeing the same things crop up, the themes for discussion will be the team approach for assessment and inspection, knowledge sharing and transfer models as a basis for postapproval, variations, changes, management, mechanisms for collaborating or cooperating in other venues.

So, again, even though the meeting, itself, is being done as part of an ICH meeting, it is being done that way with the recognition that we are putting together a strategic plan. Some of the topics that get thrown out as important elements for that plan may not really be appropriate topics

for ICH.

One of the concerns that we also have is the ICH process really hasn't allowed for very much academic input so one of the things we will also be interested in is how do we get that kind of expertise into the program or what other venues are available where we might also benefit from that kind of expertise.

Then the other items that we will be talking about; again, quality by design, product process knowledge and risk-mitigation strategies, more on principles for how you introduce and how you regulate and assess new technologies and always we come back to risk-based concepts so system-based inspections.

So I think that really gives you a pretty good flavor or the kinds of topics--these are not new. They were pretty well discussed at the April workshop. I think the real challenge for us is going to be how do we put them together into a strategic plan and then prioritize them and figure out what makes sense to work on and when.

I want to turn now, for just a moment, to a part of this that really is not very well developed but is in the thinking stages. We have a

time line for regulatory cooperation in other venues beyond ICH. What we are proposing right now is in September to report to the GMP--and this is the GMP steering committee--a plan for inviting some regulatory speakers in so we can get information about their experiences. I have listed out who those might be.

In November of 2003, we would report again to the GMP steering committee on what the various activities that we would need to undertake as a long-range plan for how we would collaborate internationally on the regulatory aspects. I think what is important here is to keep in mind that the ICH part is really about science, innovation, new technology. But there is another piece of this that really is of great interest to the regulators. So we are going to be looking at those other venues in terms of how we can deal with that regulatory piece.

Again, it seems that PIC/s might be one of the organizations that would allow that to happen. However, we do have to note, right now FDA is not a member of PIC/s so one of the things that my committee is looking into is what are the implications of membership. Do we have the

resources to become a member? What would sort of the cost-benefit analysis of that be?

In the Fall and Spring of 2004, we would want to meet with stakeholders, get outside input and then we would probably need to meet with the FDA staff on the drug-product-quality systems, its experiences with PIC/s and possible ways for regulatory authorities to collaborate.

The overall plan is in May of 2004 to develop this long-term plan that gets presented. That wouldn't happen until June of 2004. That would be a concept paper to the GMP steering committee. This is the group that Janet Woodcock chairs. We would present our plan to that group and then I think it is quite likely that, from there, it would have to be vetted further within the agency, maybe at the executive council and so forth.

But our big deliverable is to have this detailed plan by June of 2004 so that some cuts can be made on how we are going to take the other piece of this--that is the regulatory cooperation piece--beyond what is happening in the ICH program.

I thank you. I will be happy to take questions if there are any. Yes.

AUDIENCE: Could you tell us what PIC/s stands for?

MS. SHOWALTER: It stands for the Pharmaceutical Inspection Convention/Scheme. The Scheme was added later. It originally was the Convention. But then there were some legal difficulties associated with whether the European countries could participate in a convention because specific regulatory authorities were members.

At that point, they changed it to the Scheme, and it is a much more voluntary organized group of people. Previously, it had been by treaty. So that is the difference. Also, it is regulatory authority with some observership status for industry and others. Currently, FDA is one of those observers. We are not a full member.

MR. JERUSSI: Robert Jerussi, Jerussi Consulting. The question I have, listening to your presentation today, Janet; it seems to me ICH has developed almost a life of its own. It is in an expanding mode. I recall when it was going to be over after the third or fourth ICH. I wonder if there is any end in sight.

I ask this question specifically because I believe, I firmly believe, ICH has escalated drug

requirements in the United States and it has slowed and raised the cost of drug introduction.

MS. SHOWALTER: So, as I understand your question, it is is there an end in sight. I suppose I am going to have to be a little flip here and I would have to say, based upon what I have seen, no. I think the short answer is no.

Any other questions?

MR. POSKA: Rich Poska from Abbott Labs. I was wondering if you can clarify; on one of your slides you mentioned transfer models as a basis for postapproval changes. What do you mean by transfer models?

MS. SHOWALTER: That is a good question. We spent a lot of time talking around that. Basically, what we are trying to identify, and, certainly, I am not the GMP expert so I am just going to give you my two-cents worth, but what we are really talking about how information that comes in in an application, really, what we should be talking about what we think is knowledge transfer, how you transfer, in a reasonable way, what you get to the other components, stakeholders, that have a part to play in that.

So I will tell you that one of the best

documents that I have seen on that, and I don't know if you have access to it or not, is the ISPE document that they put together fairly recently that sort of goes through the various models for the kind of tech transfer, knowledge transfer, information transfer, that we are talking about as part of a quality system.

That is one of the best explanations that I have seen. In fact, I think that it is possible that we may ask that group to make some sort of presentation about that at the upcoming meeting in Brussels.

AUDIENCE: Which group are you talking about?

MS. SHOWALTER: It is ISPE.

MR. POSKA: International Society of Pharmaceutical Engineers, ispe.org.

MS. SHOWALTER: I don't recall the date of the document but it is a fairly recent document.

POSKA: I was on the steering committee and we published it last year.

Any other questions? Thank you. This is going to conclude, then, the GMP section of this. I think, in summarizing, I would just like to say "Stay tuned." There is a lot still being talked

about and worked out.

Now we are going to go into the CTD-eCTD implementation status. We have a number of speakers for that. The first speaker is going to be Justina Molzon. She is going to give CDER's perspective. Following that, Bob Yetter will give CBER's perspective. Then Christelle Anquez will talk about what is happening the other regions followed by the eCTD discussion.

Justina?

CTD/eCTD Implementation Status

CDER Perspective

MS. MOLZON: Thanks, Janet. I am just going to be giving a quick update. I know some of you have heard this presentation at DIA last week, but we have actually had an additional submission for CTD so I have updated my statistics. I think my statistics on the applications into the Center for Drugs and how it is broken down by division is basically going to be the main thrust of this discussion.

Christelle has already given you background information on ICH. I will have a couple of comments focusing ICH initiatives on its CTD efforts. I will give you an update on what we

have been doing in CDER and then, as I have already mentioned, a discussion of some of the statistics related to CDER's CTD experience.

Christelle has already mentioned how ICH works. There is a series of expert working groups, safety, efficacy, quality and regulatory communications. Regulatory communications is a catch-all category and includes the CTD efforts. These working groups work on their various documents, present them to the steering committee and the steering committee then monitors and facilitates the work of the expert working group.

Christelle already showed you this slide. It basically covers the conferences that ICH has put on in an effort to be transparent. At the fifth conference, which was in San Diego in the Year 2000, the main focus of that conference was the Common Technical Document.

So what happened the few days before that major conference was that the expert working groups on the Common Technical Documents had to work in a frenzy to finalize those documents so they could be presented at the end of the week. So you literally had groups working around the clock. CDs were being burned the Wednesday night before the

Thursday meetings. There were disclaimers on these PDF documents that they still had to be edited for consistency.

After this frenzy was over, we realized that these three groups were actually working on isolation to finish these documents for distribution. Then, after ICH-5, these documents had to be edited for consistency, numbering system, style and format.

Janet has already mentioned how, in the GMP efforts, we are trying to have more of a strategic plan. I dare say that the CTD was created in this flurry of activity and, later on, we had to figure out how to provide consistency for the various documents that had been developed by the expert working groups.

So the reality of implementation is that, once the regulators start preparing these documents for publication, in our case, the Federal Register, or posting it on our web, we realized how complicated they were and we were faced with the enormous task of making them consistent.

This, along with the fact that regulators have different systems for implementations meant that, no matter how closely we worked together,

there were still going to be some minor inconsistencies. But these minor inconsistencies do not tract from the enormous work that has been done on the Common Technical Document, and the Common Technical Document should be as clear as possible.

So we have been devoting, along with Europe and Japan, much effort to do away with these ambiguities and inconsistencies at our ICH meetings. This is a continuous process and I believe that CTD has evolved and improved over time.

Many of you have seen this very simple diagram. This is how the CTD was initially presented. It has now evolved in a more complicated presentation based on discussions we have had at various meetings such as DIA raps or these open public hearings. We understood that people did not understand whether documents needed to be layered or stacked. So we added a numeric numbering system to indicate how we wanted these documents to be assembled. So outreach programs and discussions with our stakeholders have led us to clarify some of these issues.

The truth is we really need experience

with the documents and submissions will help industry and regulators to gain familiarity with the new CTD format. As I have already mentioned, meetings and discussions are helpful in improving these documents.

But because you needed experience with the documents to help implement them, the voluntary-submission phase was extended from July of 2002 to July 2003. So we added an extra year so there could be more experience on the regulator side and also on the industry side with these documents.

One thing that comes up at all of these public meetings is, someone asked, "Well, I thought the CTD was supposed to be same and now we have to do these differences." I need to point out that the Common Technical Document is not a global dossier, so a very common misunderstanding by those not involved in the ICH process.

The submissions contents is different for the U.S., EU and Japan. This is because there are still individual regulations in those countries that have never been discussed in ICH. They were either too contentious or industry, who generally proposes concept papers for topics, they just were

not proposed or they weren't taken up.

So the Common Technical Document is an agreed-upon format for the modular presentation of summaries, reports and data. It incorporates the relevant ICH guidelines as building blocks and puts them in the same order for submission to ICH regions. So we have had over fifty ICH guidelines. All the Common Technical Document does is stack them in the same order so they are in the same order for Europe, Japan and the U.S.

This question was also addressed in the Q&A process that has developed to help clarify some of the issues related to the Common Technical Document. So the very first question under the CTD general questions was, "Will a dossier using the CTD format, Modules 2 to 5, be identical for all regions?"

The answer was, "Not necessarily." The CTD provides a common format for the submission of information to the regulator authorities in the three ICH regions. However, the CTD does not address the content of submissions. This is in terms of regional requirements and sometimes applicants have different preferences for indications, dosage forms or whatever so there

could be a difference.

To help those submitting NDAs, BLAs, ANDAs, et cetera, to the FDA, we created a draft general considerations guidance called Submitting Marketing Applications According to the ICH CTD Format. This was posted in September of 2001. Originally, there was a comment period until November of 2001. Only twelve sets of comments were submitted. This was generally based on people just reading the documents after they were posted on our web.

I point out that comments are always welcome but to encourage comments from companies that have experience assembling these documents, I reopened the document until June 16 of 2003. That was just last week. So we are going to be collecting any additional comments. However, I just note that two weeks ago, I went to the docket and looked and there still were not any additional comments.

But we will incorporate comments from the steering committee, expert working groups and meetings such as this into our final draft of the general considerations document. So, please, send us your comments.

We also have established a web for electronic submissions called esub@cder.fda.gov and also cdt@cder.fda.gov. So you can send comments directly in to the FDA. We are trying to consolidate those comments. If you have very specific questions about your applications, they come in to either the esub or the CTD e-mail address. They are reviewed by basically the same person and then we come up with a consensus response.

Questions that would help the overall CTD process are taking to the ICH steering committee and expert working group meetings. So we have a few that we can take to Brussels in a couple of weeks.

What I really wanted to focus on during this presentation is exactly what is the experience that CDER has had with applications. So far, we have had twenty-five submissions. We received one when I was at DIA. I gave a presentation at DIA, a cohort of twenty-four. But now I can say twenty-five.

I have broken these submissions down by Office of Drug Evaluations I through V. So you can see that ODE I, Neuropharm, has had two. Oncology

has had three. The asterisks here indicate that there were three NME submissions to Oncology. Two to Cardiorenal. In ODE II, Metabolic and Endocrine had three. This is where there was a change. Originally, just last week, there were two. We just received one a couple of days ago.

So that provided for an additional NME so there are two NMEs. In Pulmonary, there are four. There are none in Anesthetic, Critical Care and Addiction Drug Products, none in Gastrointestinal and Coagulation Drug Products, three in Repro and Urological Drug Products, none in Medical Imaging, one in Antiinfective, two in Antiviral, two in Special Pathogens, and there are two NMEs in Ode V. There are three in Analgesic and Ophthalmic, none in Derm and Dental and none in OTC.

I just read those out for the transcript, so I'm sorry. I am sure you could have read all this yourself but I am trying to document the submissions.

If you look at distribution between the Offices of Drug Evaluation, it is really not that much different. There is just a scattering with ODE I and II having seven each.

If you look at the time frames,

considering that the CTD was accepted by regulators as of July 2001, I have broken these down into half years since then. So, from July to December of 2001, there were five CTD submissions; January 2002 to June 2002, three; July 2002 to December 2002, nine; and then January 2003 to June 2003, eight, with a total of twenty-five.

So, if you plot this out, you will see that the second half of the year 2001 to the second half of the year 2002, there has been an increase. The same from January to June of 2002 to January to June 2003. So there has been an increase. We then broke these out by months so you could get an idea of how these are submitted. We will get one. Then we won't get any. Then we will get one, skip a month. So it is just a scattering.

It was sort of predictable that, in December of 2002, we had more because people gear submissions toward the end of the year.

So, so far, there have been twenty-five submissions in CTD format submitted to ten different review divisions. All five offices, ODE I through V, have had experience and that experience is in terms of hybrids which is either just the safety module submitted in CTD

format--that is the pharm-tox information--or the quality modules just submitted in the CTD format. Then the rest of the application would be an NDA or a BLA in Bob's case.

New dosage forms was another CTD type of submission, new indications. and then NMEs or complete CTDs. So what I did to further delineate on experience, I looked at a typical NDA review team which is project manager, the medical officer, chemist, statistician, pharmacologist, pharmacokineticist, clinical microbiologist and a microbiologist.

I just tried to plot the exposure for each of these types of submissions. So, for a pharm-tox hybrid, the project manager and the pharmacologist would have experience. For a quality hybrid--that is just the CMC section in CTD format, project manager, chemist and a microbiologist, perhaps. For a new dosage form, once again, project manager, chemist, but a pharmacokineticist might be involved if it from a tablet to a capsule or vice versa and then a microbiologist for sterility issues.

For a new indication, project manager. You would be involving the medical officer and, perhaps, a statistician, the pharmacokineticist and

possibly the clinical microbiologist if it had to do with an antiinfective or antibacterial product.

Then, for a new combination, you have included more and then, finally, for an NME, the entire review team would be exposed to the common technical document.

So the good news about these submissions are that there were no "refuse-to-file's". These were not perfect submissions but they could be reviewed. I should note that CDER has been flexible during this voluntary submission phase because we wanted to encourage submission of these documents so we could gain experience.

In terms of the number of companies submitting these documents, there have been nineteen different companies. Several of them have submitted two or three submission in CTD format. Breaking the companies down, there were nine large PhRMA companies, six mid-size companies, four small companies that had just one or two application overall and then the World Health Organization also submitted an application.

On July 1 of 2003, the Common Technical Document will become mandatory in the European Union and Japan. It will be highly recommended by

the FDA. The reason it is highly recommended instead of mandatory is that ICH documents have always been considered guidance by the FDA. Good guidance practices, or GGPs, require that the CTD not be mandatory.

So this is not an indication of lack of commitment. It is just that our good guidance practices indication that these documents have to be guidance and not mandatory. So, presubmission meetings indicate that many companies are following this recommendation.

In terms of presubmission meetings, this is an indication of the next wave of CTDs that will be submitted. I have been invited to twenty-one presubmission meetings for CTD-formatted NDAs. I generally go to a presubmission meeting with staff from Dr. Randy Levin's group, the Office of Information Management, so that we are available to the Review Division just to answer questions on the Common Technical Document because, if the reviewers have not received one to that date, we have a basis of experience that can help them.

We are also available to help sponsors with questions on how the documents should be formatted. As I have already mentioned, with the

esub and ctd e-mail addresses, we are trying to collect areas of concern and issues that require clarification.

At the presubmission meetings, the sponsors were advised to follow the updated information on the ICH web which is www.ich.org. Because of our good guidance practices, it takes a while for our editors to convert the ICH-harmonized documents into the GGP-prescribed format. I also tell the sponsors that they should look at the ICH website just to check up on the Q&As that have been updated after each of the ICH meetings because these are helpful in assembling the CTD-formatted submissions because, often, another company has had the same issue that you are concerned about and there has been a coordinated consensus response in terms of the CTD disciplines. The Q&As are set out in terms of safety questions, efficacy questions, quality questions and then just general questions.

Basically, the specific information that is relayed at these presubmission meetings are; do not modify the CTD table of contents, submissions should exactly match the CTD, provide all information under CTD-ICH-negotiated headings and numbers, do not create new headings or numbers.

I have basically tried to say the same thing four different ways so people realize that you really should not modify the headers and numbers in the CTD format because that is what it is. You can't change or modify the numbers or headers in any way.

Additionally, if a company does not have information for the section, provide the ICH CTD number and header and then put "non applicable," or some other language. Don't skip or delete sections and never renumber sections. I have actually seen applications where someone just left something out and then went on with different numbers. So they had to redo their numbering system because that just wouldn't help them in the process because the numbers have to be the same and the headers have to be the same as the ICH CTD documents.

At the ICH meetings last February in Chiba, Japan, additional sets of Q&As were endorsed by the steering committee and were posted on the ICH website. Some of these were related to general matters but some were also very specific. There was a very lengthy discussion of the ISS and the ISE and the need to include it in the CTD in some manner.

But the meetings also focused on the eCTD which you are going to hearing about later from Tim or Randy. I always recommend that companies check the ich.org website after ICH meetings for the most recent information. So we are going to be going through the same process in Brussels. We will go over Q&As that have been proposed. We will try and finish up any problems that are still remaining in terms of confusion or clarification with the CTD.

So the next steps for CDER are we are going to continue to meet with project managers for feedback on CTD submissions. Increased submissions will help determine the effects on the review process, if any. This may help organizes reviews and reviewers a little bit more.

Presubmission meetings indicate more CTDs are on the way. CDER is looking forward to receiving submissions so that both industry and regulators can experience the CTD format. So we have a nice cumulative curve developed and I would just like to see many more submissions.

Thank you very much for your attention.

Are there any questions?

MR. MILLER: Loren Miller, PPD. The question I had as, of the submissions you have had,

how many were electronic and, secondly, of the full submissions, how many required a separate ISS or ISE that was taken out of the context of the--

MS. MOLZON: In terms of electronic, there has been a mixture. Some of the applications would come in according to the eNDA procedure but then the CTD portion would be in paper. So, depending on the company and the approach, there was a nice mixture. So we are going to be looking into those statistics. I haven't broken things down to that extent.

In terms of the ISS-ISE, there has been a variety of approaches. Dr. Temple did a very nice presentation at DIA which will be posted. All of the DIA presentations from CDER will be posted on the website. It is just depending on the type of application you have and it is basically if the documents you have put together for ISS-ISE requirement can fit into the overview and the summary, then you do that. If not, you are going to have to put some of the narrative in those sections and then the data in Module 5.

So it is really a case-by-case situation based on the size of the submission and the type of documentation you are providing.

MR. POSKA: Rich Poska, again, from Abbott. You mentioned that, and I recognize that the CTD is only intended to provide a common format, but in your presentation you mention that it does not address the content of the submission because of regional requirements and regulations.

However, the previous presentation that we had did talk about some initiatives that the FDA is working on towards trying to harmonize certain things. You talked about the concept paper on specifications. I think one of the largest benefits we can get out of CTD is, at least from an industry standpoint, to try to get harmonized requirements and specifications.

So my question is, should we expect to see the long-awaited stability guidance from the FDA to be incorporating more ICH and less regional type requirements that will be more or less transparent or will it still contain inconsistencies with the ICH and require us to have separate sections for global applications.

MS. MOLZON: I have a major disclaimer. I am not in the Office of New Drugs and I haven't seen the stability guidance. As I said, this is the beginning and things are evolving. It is hard

to imagine exactly what is going to go on in GMPs. All these things are up for discussion. So you have started the framework. So now you have some additional topics to talk about.

This is where we are right now. It would be nice to move towards more harmonized, but I can't predict that.

MS. SHOWALTER: One comment about that is that, at every ICH meeting, there is now a section where we talk about implementation issues. For things like stability, and there is actually a mechanism for getting this aired internationally--and I think it is an important component of the program, as we move more into an implementation phase.

So what I would do--and the vehicle for making all of that happen is really through PhRMA. So I would encourage, for those kinds of issues to be taken up within PhRMA and then they should be put on the table.

There is a time line involved in this. It is too late for the Brussels meeting. Basically, the way you want it come up is you want it to be very well defined and described in a paper that PhRMA, then, could float hopefully, if it is with

FDA, to FDA first or if it is with Europe, to Europe first.

But then, if the issue can't be resolved or is not resolvable, then it really should be taken up as an ICH implementation issue. We actually encourage that. So there is a procedure put in place pretty much heretofore that has been empty. That section hasn't been discussed because nobody floats anything.

It is sort of interesting to me. Prior to us taking that one, there seem to be all kinds of implementation issues. But, once we put it on the program as a specific agenda item, they just went away. But I would encourage steps to be taken to make that happen because we really should be taking about implementation issues.

If we want to preserve what we have already achieved, we have to do that as well. And we understand that. So we would encourage that.

I just have a quick question. Is the flexibility going to remain the same or will it change as of the first of July?

MS. MOLZON: No; we are always flexible, in my opinion. You are submitting these documents and good guidance practices are very helpful in

this situation. Because these documents are not mandatory, we allow leeway for discussion between the sponsor and the Review Division as to how they want things put together.

But the headers and the numbering systems, there is no negotiating on that. That is not flexible. We were flexible in just discussing with the sponsors on how the documents were put together and we are going to be less flexible in terms of numbers and headers.

We were just trying to get the sponsors used to these formats. But now they have to adhere to the numbers and the headers.

MS. SHOWALTER: Thank you.

The next speaker will Bob Yetter and he will provide CBER's perspective on the Common Technical Document.

CBER Perspective

MR. YETTER: Good morning. It is a pleasure to be here. I hope you will bear with me a little bit. I am not quite as recovered from a sinus infection as I had hoped I would be by now.

Justina told you about CDER's CTD implementation plan and, to a great extent, it reflects the FDA's implementation plan. You have

seen this consensus diagram of what the CTD is all about. The process that we have undergone in CBER looks very much like CDER's. It involves publishing and revising guidances as needed, addressing certain administrative issues, training staff and outreach to the industry.

The primary guidance involved is the one that Justina mentioned earlier, the general guidance on submitting marketing application in ICH CTD format. That one has an introduction and background, talks about the CTD format, itself, provides considerable information on Module 1 and general issues for submissions. All of that is very important for people being able to use that.

We have extended the comment period. It has again closed but we extended the comment period until June 16 to get further comment once people got some experience with working with the CTD so that we could find out where the problems were, where the issues were.

We will use those comments that we got in and revise the guidance and get out a final guidance. In CBER, we instituted what would be called an administrative issues subgroup to address certain problems or to make sure that there were

not certain problems. What it was intended to address was concerns surrounding receiving, reviewing, processing and archiving applications in the CTD format.

They were supposed to look at needs for a smooth transition and predict potential difficulties and identify any remedies for the difficulties and identify training needs.

Applicability and scope; I am going to mention this because recently, with other initiatives, these questions have come up. ICH was originally intended to address pharmaceutical products and specified biotechnology products. CBER has a variety of products including specified biotechnology products that fit within the ICH definition. But, as of the end of this week, the majority of those specified biotech products will be transferred to the Center for Drugs.

That has raised the question of where is the Center for Biologics in terms of implementation? What is going to happen with the CTD for CBER if most of the products that this was intended, originally intended, to be applied to, will transfer?

I am going to go back to what that

administrative issues subgroup found out. They went off to work with their respective offices and really identified no major issues for the implementation of the common technical document. There were no serious concerns about receiving them. There were no serious concerns about reviewing them and certainly no concerns about archiving them.

They looked at the potential benefits of the CTD for CBER. Increased harmonization between the NDA and BLA; now, that is something we have been directed to do since FDAMA in 1997. Increased consistency between applications; one of the biggest problems that we have is that every BLA that comes in, because there is no real prescribed format in regulation for a BLA, every BLA that comes in is unique.

This provides us more consistency in what will be coming in. It will facilitate communication within the FDA and between CBER and the sponsors, we believe. So it is a more predictable format which would allow for more consistent reviews and easier analysis across applications, something that we frequently do to try and predict trends and develop guidance

documents to provide industry more information on what we expect. In other words, we go back and look across applications to see where things are not clear to industry. This is going to make that effort easier.

So where does that leave CBER with respect to the CTD? We intend to continue to implement the CTD for our products, all of our products that are licensed. We will apply it to vaccines. We will apply it to the biotech products that are not transferring and we will apply it to the licensed products that remain in CBER, the traditional biologics.

We have to date, and I haven't got all of the wonderful statistics that Justina had on what we have received, but we have received, in complete CTD format, fewer than ten new applications or supplements. I don't have any numbers on how many partial CTD submissions we have gotten.

One of the difficulties in assessing this is that we have not actually gotten a CTD in paper. All of these have been fitted into our current electronic BLA submission paradigm. They have all come in electronically. Had they been printed out, they would have been nice paper CTDs. But they

don't actually take a true CTD format because they are fit into the current eBLA submission approach.

Now, as the eCTD becomes available, we expect that those will be submitted in the proper eCTD format and we will begin to gain experience with that.

So that is where we are with implementation of the CTD in the Center for Biologics. I would happy to entertain any questions.

MS. GAWRYLEWSKI: Helle Gawrylewski, J&JPRD. You both mentioned that the comment period for the general considerations document was closed but Justina intimated that comments would still be accepted. Is that true both for CBER and CDER? What would be the window of opportunity to submit additional comments?

YETTER: As a fact of the good guidance practices, you may comment on any guidance document at any time.

MS. SHOWALTER: Thank you, Bob. Next on the agenda, Christelle is going to give you just a few brief comments about what we have learned that is happening in the other regions with respect to the Common Technical Document.

Other Regional Perspectives

MS. ANQUEZ: I will give you a brief update on the CTD implementation that we authorize in the three regions, Europe, Japan and Canada. I don't have slides for this. I'm sorry.

As you know, the three regions are getting ready for the July deadline which is the time when the CTD will be mandatory in Europe and Japan and strongly recommended in Canada.

In Europe, they received twenty-six submissions using the CTD format of which sixteen are in full CTD format and six are in mixed CTD and old Europe dossier format.

Among these twenty-six applications, there are six on biotech products and twenty-one on new chemical entities. Japan received sixteen submissions in CTD format, five for biologics and biotech products and eleven for chemical drugs. Among the submissions for chemical drugs, five were for already approved drugs, one for a combination process and five for new chemical entities, new drug applications.

The Japanese have already had three meetings with JPMA, their pharmaceutical industry association, to explain how to compile CTD

documents in April, 2003. Following this meeting, Matilda Bilieu is planning to publish within the next month a notification about the revised CTD guideline document as well as a Q&A document which contains Q&A agreed on in the ICH meeting in Tokyo in February.

In Canada, they have been very actively preparing for the July 1 deadline, as you will see. They received sixty submissions in CTD format, fifty for chemical entities of which thirteen were for new drug submissions, twelve for supplemental new drug submissions and twenty-three for abbreviated submissions.

The ten remaining concerned biologics and radiopharmaceuticals. Health Canada had two sessions with industry in late April and, following these, they revised a number of guidances. They revised the general filing guidance to take into account the most recent ICH decisions and guidance. They also prepared a revised guidance on the filing of bioequivalence studies in the CTD format that includes a description of how such information should be filed within the E3 framework. They should permit the use of the clinical-study report for general application.

Health Canada also prepares quality guidances to assist sponsors in the filing of applications for vaccines, conventional biologics and blood products. A similar guidance is also near completion for radiopharmaceuticals. They also revised the drug guidance on biotech products.

All these guidances will remain as drafts until the fall. This will allow them to incorporate other amendments following up the discussions which will occur in Brussels.

The notice and all these accompanying document guidances will be posted by next Friday on the Health Canada website. Lastly, the original Q&A will be published in conjunction with the ICH CTD Q&A after the Brussels meeting.

Thank you.

MS. SHOWALTER: Thank you, Christelle.

The next presentation will be on the eCTD and Tim Mahoney is going to provide that.

eCTD

MR. MAHONEY: Good morning. Thank you for coming to sunny Washington, D.C. Every day is sunny here--at least today is, anyway. I am here to talk about the eCTD. We have been pretty busy in the FDA and in the eCTD Implementation Working

Group because we are now an implementation working group. We are not just an expert working group. So we are working on implementing the eCTD in the three regions.

I am going to focus primarily on what we are doing in the FDA in the U.S. but let you know what we are going to talk about in a few weeks in Brussels.

I am not sure of your background, what you know about the eCTD. Are you familiar with it? I started to become familiar with it in August and there are a lot of acronyms; eCTD, CTD, ICH, ETB, all those different things. I don't know what your background is. So I will explain the eCTD a little bit.

There has been some mention of, and Justina mentioned, CTDs coming in with some electronic components. There is a very clear distinction between the ICH eCTD and an electronic eCTD. They are not the same. They are very, very different so we need a way to view eCTDs. I am going to tell you how we will do that and when as well as the next steps for both the FDA and ICH eCTD IWG and where you can get more infection.

The eCTD is an ICH specification,

obviously. This is an ICH public meeting. To be implemented in the U.S., EU, Japan as well as Health Canada has a very strong interest in implementing the eCTD and harmonizing with the FDA. It is not a content function. The eCTD IWG doesn't address content. We take the CTD and transfer it electronically from applicant to regulator so we are not a content group.

But what it does for the FDA and for the other regions is it provides first and foremost a cumulative view, a table-of-contents view, rather than the folder-file structure that you may be familiar submitting in the U.S. This will be a cumulative view so, as your submissions come in for an overall market application, a cumulative view will be built. And it is consistent.

That was addressed a little bit earlier, but it is the same table of contents and the eCTD is not flexible at all. There are rules to submitting an eCTD, not FDA rules but technology rules. So you have to follow what is called the document-type definition in order for this to work. But what it will also provide is a consistent table of contents for both you building it and our reviewers reviewing it for INDs, NDAs, BLAs, ANDAs,

DDMAC promotional material and everything, if you have read the draft U.S. Module 1, all the different components in there.

So you will be doing the same thing. Our reviewer will be looking for the same information across all these different types of marketing applications. Its components mirror the CTD. It is actually taken directly from it. Module 1 is defined in each region. The U.S. has a draft Module 1 ready to go. Modules 2 through 5, their content is defined in ICH. So, for those of you were not quite familiar with the eCTD, hopefully that helps a little bit. How is the FDA going to let you know what we are doing here? A lot of the eCTD specification leaves things open to regional guidance. It really wasn't that we were running out of time in the working group and said, "We will just regional guidance." It was really that there are distinctions. Justina made a really good point. This is not a global submission but it is a common format for submitting in the three regions.

Some of those things, especially when you take PDF files and use them in Japan, there are distinct differences. So there are going to be some differences across the regions but the

technology is the same.

The FDA has released eCTD specifications. They support a soon-to-be-published eCTD guidance. You may have recently seen an eCTD guidance and that was really just the local publication of the Step 4 eCTD specification. But this week, as a matter of fact yesterday, on the website you see up there, www.fda.gov/cder/regulatory/ersr, we published a series of specifications that fill in the technical blanks for eCTD implementation in the U.S., particularly Module 1. It is not just a document-type definition file. It is a narrative.

Modules 2 through 5, study reports, which is an interesting topic, one that we have sort of bounced around in ICH. The Step-4 eCTD specification was signed and then we received comments that it really doesn't provide the structure for study reports that the CTD references. So we have had some debates and some good conversations and some harmonization in the eCTD IWG.

That has resulted so far in what is called the study tag-in file which is a way for you to follow the eCTD Step-4 specification as well as provide the granularity in the structure that we

need for those study reports.

XML is the technology you use to create and eCTD. If any of you here are not coders or developers, then you have absolutely no need to understand XML. You are not going to have to. But what they call it is human-readable XML. I don't know if that is really the case. If you have ever tried to read XML, you are still human but it is not as readable.

So we have a real human readable overall FDA eCTD table of contents published on there as well. And we welcome comments. Now, the draft guidance is making its way, per our good guidance practices, through the different centers affected. This is a combined CBER-CDER project, as Dr. Yetter mentioned. But these specifications can help particularly the technical folks that are going to help you prepare an eCTD.

These are all posed on a website that gives suggestions for the steps to submit in an eCTD. Step 1 is to read all of that. Then, when you are done in October reading all that, get back to us and let us know when you are planning an eCTD. The technology is new. It is new for you. It is new for the FDA so we want to make sure that

there is a good dialogue going.

The esub e-mail that Justina mentioned is the place to go. Let them know exactly when so we can prepare on our end getting the training in place for reviewers and also getting ready to test your sample and make sure that it will display the way you want for the reviewers.

It won't be a real labor-intensive process. It will be just exchanging small files for any of the quick tests and getting back to you saying, "Hey; everything looks okay," when we are finally done. Then you will be ready to submit.

I will leave this up for a moment so you can write that down. This is part of the U.S. Module 1 DTD, document type definition. It is pretty clear with the leaf content in there. Up to this point, a lot of concentration has been on the XML. That really shouldn't be the case. That should be left to the technical folks. It is, what does the XML do. Here is more of that U.S. Module 1.

Building that cumulative table-of-contents view, giving us the ability for life-cycle management to reference across different submissions. That is what you need to know about

the XML. You don't need to know what an href or what a leaf--well, a leaf, you may. But you don't have to know XML, just the ability it gives both you and us. That is why this is important to you.

This isn't just going to help our reviewers, but if you can archive and store and generate your information standard across many different application types and then across many different regions, that initial up-front investment will return pretty quickly to you.

A little bit better, a little more human readable description of the U.S. Module 1 for the eCTD contains this information. I won't run through the entire list because the information is up on the web and you can take your time and disseminate it.

But there is a good bit of information. And it does allow for submitting electronic INDs. Particularly CBER has had an electronic IND guidance out there but CDER has been waiting for the eCTD. And it is finally here.

So how are we going to view these, all that gobbledegook you saw on the U.S. Module 1 there? What we are using to start off with is an internally developed system called the eCTD Viewer

System. It is a combined CDER-CBER project. If you remember Dr. Levin, particularly John Clark, Nike Ya, several years ago presented the Cumulative Table of Contents Viewer. It was really a few chemists were trying to solve a need, that cumulative view need.

That is the prototype that we built the system on so it looks a lot like it but it is meant for production across the two centers. It is built by reviewers. I work in an IT shop and content is something I don't know much about when it comes to the science of what we do at the FDA. How they want to view it, also, I wouldn't know much about. So reviewers build the system. They define the prototype and the production system. We just take care of the technical end.

They approve all change requests or a configuration-control board. So they are actively involved. They are also part of our outreach plan, so we are going around to the particular divisions right now from those CCB members presenting the viewer.

The initial functions we are going to have in the FDA, all of the things I mentioned about the eCTD that it will let us do, we would develop over

time. Some of them we need to gain more experience on, but view, navigate and download. The system is in production. It works. It is in both CDER and CBER. If an eCTD were to be submitted today, and it was created correctly, we could process it and view it in each center. Technically, we are ready.

We spend a lot of time going through requirements gathering, doing use cases and all these other different methodologies you may not be familiar with. We also identified additional requirements that really we need a little more time with the eCTD to develop, particularly, preferences, quick access to an area of an eCTD, searching and book marking.

A lot of that is going to be CTD as well as eCTD education, so as we get experience with them, we will add that functionality. So what do we need? We need guidance and we need specifications. The draft guidance is ready for internal sign-off and the specifications are posted. So we can almost check that one off.

We need a system. That one is installed and being configured. We can check that off. And we need outreach. We need to let everyone know how to do this. We are in the middle of that. We are

supporting internally our reviewers, those that support the reviewers and the technical staff. We are working with Dr. Levin's Office of Information Management to provide just-in-time training.

So, when you let us know you are submitting an eCTD, we will guarantee that the reviewers are trained. If you don't let us know, we can't guarantee that. So training is a big part of the internal and external as well. And then maintaining the system.

So what we are doing now; we have a couple of small change requests on the system but we are doing a lot of outreach. Presentations to divisions--and they have been very positive. Even those reviewers that really hold on to paper and don't want to let it go see the power that the eCTD provides them with that first cumulative table-of-contents view. It is really a tradeoff, and it is a good tradeoff to the eCTD.

We are preparing for eCTD. I already went over these steps. We are going to watch this. We are going to maintain both the eCTD specification in ICH and our system internally at the FDA. Part of that is the next meeting in a few weeks. The agenda in change control. Technology cannot remain

static.

You may be familiar with a word called "shelfware." So you spend a lot of time and they spent years developing the ICH. If there is no process in place to control change, it become obsolete. Really, none of that existed in ICH. So, after Step 4, the first thing we did was develop a change-control process.

A lot of technology is guessing until you start implementing. Then it is going to change. So we need a way to prioritize, first accept, then prioritize and address change requests. One of the first one is that study report. That will be one of the first things we talk about, showing our examples in the U.S. with the study tag-in file.

There may be a different future down the line for study reports in the eCTD but, for now, the study tag-in file is the way the FDA is going. We are releasing a comment style sheet for those that don't have eCTD-viewing software. It is very similar to a web browser. It provides the content and will give you a common view between the regulator and applicant.

So the FDA has created it. We took the burden on ourselves to create it and will present

it with our partners' approval to the steering committee next month.

Another thing we need to think about are DTT releases. Those of you here from software developers, this is of particular importance to you. One thing that our PhRMA partners that we work on, they get nervous with every meeting because they don't quite know what is going to happen. If there is an industry out there building eCTD software, we can't do that, too. So we are going to talk about scheduled releases of DTT changes as they reflect changes in content to the CTD or changes in technology.

We are also the M2 expert working group. As that, we have been tasked to look at technology. Recommendations we have made in the past, which are outdated, include media types. Then we need to confirm our ICH-6 topics and speakers.

So what we are going to do at the FDA, we are going to be future versions of the eCTD viewer. We are not a software development company in the FDA. So, if someone else is out there doing it better, cheaper, faster, we will take a look at it. So part of that is doing alternatives analysis on those commercial products that can be used to meet

our needs for viewing and processing eCTDs.

For those of you who would like to see what we are doing, we are going to put it out there this summer. We will post our eCTD viewer and related documentation and you can do whatever you want with it, except complain about the way it was developed over and over again. So, we won't be able to trouble shoot if you want to install it in your own environment, but we have pretty good documentation. It is all CMM Level-3 documentation. So you should be able to do it.

More information; esub@cder.fda.gov. That is a great place to go. Really, if you send me an e-mail, I am about 348 behind so get in line. But esub always responds. Part of our change-control process in ICH is filling out change-request forms. If you notice something wrong with the eCTD specification, something is missing or even if you have a general question, in the CTD page, along with the eCTD specification, is a change-request form as well as those change requests that we have already identified.

So, if you see something up there already, we are working on it and we will get to it as soon as we can. If you have any from the U.S. that you

want to send, you can send them directly to me at that e-mail. I will do them quickly if you are trying to make the July meeting, as within the next hour.

So thank you for your time. Can I ask are there questions? What are your questions before I step down?

MS. GAWRYLEWSKI: Helle Gawrylewski, J&JPRD. I have a question about the study-tagging files. So FDA has a proposal and you are taking it to the M2 expert working group. I understand there will be some discussing and arguing about that specific element of the eCTD proposal. What is the mechanism to propose alternative ways of doing this study-tagging at this point, realistic mechanisms?

My second question is when did you post all of this at the website because I looked yesterday and I didn't see anything new. Was it late?

MR. MAHONEY: It was late.

MS. GAWRYLEWSKI: It was late?

MR. MAHONEY: Late for us in the government. It was about 3:30. That is a good question. The study-tagging file, the good thing about our change-control process that I mentioned

is we don't argue. We do discuss, though. Arguments really go nowhere so we needed a process to disseminate information.

There was a fact. The FDA needed a level structure. There is a sample up there now. Our original proposal has been up there for a while for study reports. It has been up on the ICH website next to the eCTD specification. Including that in the backbone, we couldn't get consensus in February, or even before February and we did a lot of work.

So the options were limited. It was the FDA will either bring this--is this an ICH topic or is it regional? If it is regional, we will go off and we will figure out the best way to do it without breaking the specification we agreed to.

But we wanted to keep it in ICH because we understand, the technology has a ripple effect and you can't just go off and do whatever you want. So we keep bringing it to ICH. What we found in February was that the JPMA folks had a solution that worked. We had consensus from the group as part of our change-request process. I wish I had brought the diagram, but it shows there are two different ways that a change request is deferred.

One is just because we didn't have the time. The other is because we need more information.

The study-tagging file is one of those where we need more information about it. So the FDA is implementing this study-tagging file solution in the U.S. As far as the ICH goes, we will report at each meeting but if someone wants to bring up the request, which they have, of including this information in the eCTD backbone, we will listen but I don't know if it is going to be our argument anymore because we have gone down that path already.

So when the other five partners are ready, then we will move to put it into the backbone. But we have given them about all the information they need. But, if you have alternative recommendations, we would love to hear them. The last thing you want to do in technology is be closed. So you can feel free to send those directly to me. And it is never too late.

Thank you.

MR. JERUSSI: Robert Jerussi from Jerussi Consulting. I have a general question, not just on the eCTD but any CTD. Since it is a voluntary submission in the United States, do you really see

a lot of companies submitting it? I mean, as a consultant, the question I get, should we submit an application in a CTD format. And I say, "Well, it is not required."

The other thing I say is it requires you to submit more information, and a lot more. A pharmaceutical development report for both the drug substance and for the drug product, a summary section which allows importation from other sections of Module 3. So those are a couple of things that are required; in other words, it is more information.

Why would a firm voluntarily submit that? To give you an example, there is a drug-product guidance out now. I think the comments are due by the end of this week, seven-and-a-half pages of it. 14 percent is devoted to pharmaceutical development documents.

Why would a firm want to submit that and expose themselves to any number of questions? So I ask, am I all wet? Have I missed the boat? Is the CTD easier or does it really require more information, require companies to subject themselves to a greater scrutiny at the headquarters because development documents were

always required, but they were at the plant and the investigators would look at them.

So it is not just for you. It is for anybody.

MR. MAHONEY: I can, I think, tackle all of that. No; I can tackle the eCTD part of it. You haven't missed the boat but the horn is sounding on the eCTD. That is a great question; why would you do it.

My question is why wouldn't you? Why would you take the time to have an infrastructure that supports three different technologies in three different regions or spend the time in investing, on building a submission in an electronic format that is not consistent?

So, for the electronic part of the eCTD, you can develop your infrastructure. I know the FDA has pretty good IT costs. They are not skyrocketing but I know, from talking to my counterparts in PhRMA, that their IT costs are astronomical. They want the eCTD because then they build one infrastructure that supports one way to submit for INDS, ANDAs, NDAs, BLAs and the FDA as well as the other regions. So it is consistency.

Everything is called this, this, this and

this every time. So that is the benefit electronically. I will pass off the scientific contents to some of the other experts here for the answer on that one.

YETTER: Do we expect the industry to submit in CTD format? Yes; I think that the industry is going to. I think there are benefits to the industry. The benefits that we perceive for CBER, I think, are benefits that also pertain to the industry as well. Does the CTD actually require more information than would be required in an NDA or a BLA? Not really.

One of the things that you are seeing is the evolution of regulatory process. There is not more information being requested. It may be organized differently. It may not look like what you are used to seeing. But I don't believe it is really requesting more information, to a great extent.

We would be happy to entertain comments to that extent on any of the guidance documents that you see or even in fora like this. But, right now, we are in the process of revising some of our CMC documents to conform to CTD. We don't see ourselves increasing the amount of information we

are asking for.

We are asking you to put it in a particular place, but we are not asking you to duplicate things. In fact, if anything, this will allow us to decrease needless duplication much the way we achieved when we eliminated the establishment license application.

MS. MOLZON: Just to repeat what Bob said. All we are asking to be submitted is an NDA in CTD format. Dr. Jerussi knows that ICH is a joint initiative between regulators and industry and the working groups involve industry as well as regulators. Industry proposed the common technical document and had to go through a number of feasibility studies before the regulator would even take the topic up.

In the discussions, there is a consensus on these topics so industry is at the table negotiating these. Then, when consensus is reached, the document is published for comment and it goes through the ICH process. So industry helped develop these documents, Dr. Jerussi, so I am having a difficult time understanding why you are saying why would industry do this when they are the ones that proposed this to begin with.

MR. JERUSSI: I was not present at that meeting, the mid-May DIA meeting, which spoke about this business of the pharmaceutical development report. But, according to the trade press, a number of company representatives, and I don't know whether they were generic or PhRMA companies, got up and voiced strong objection to submitting that kind of information in a document.

So it is not just my thought. There are people in the industry who are saying, "Why does FDA want a pharmaceutical development report for the API for the drug product, which is new--this was never required in an NDA. I don't know about BLAs. Not only that, there is even more to it than that. It is the whole business of how did you develop this? What difference does it make how a company develops something as long as they developed it.

It has to be the drug that meets the requirements of the agency, is efficacious, is safe. It doesn't really make any difference how they developed it.

Now, the industry may find this but I don't know--when I was involved with ICH, the generic-drug industry was left out. They got

saddled with a number of requirements. Now, I know they are observers, I believe, now. But I don't know if they are really in on this. But I do get these questions.

MS. SHOWALTER: Actually, I think we are sort of moving from the strict CTD response to we are now sort of getting into the area that I talked about at the beginning with respect to the GMP, the drug product-quality program. So we are kind of blurring the lines a little bit here, which is okay because I think this is sort of how the discussion is evolving. But we are getting into some uncharted territory a little bit.

I think what Justina and Bob correctly are referring to is the fact that--and they have correctly characterized what we have done with the CTD and how it came to pass and so forth. When you start talking about pharmaceutical development, one of the things I mentioned is that is probably going to be endorsed as an ICH topic at the meeting in Brussels.

It really relates back to the GMP part of the ICH program. I think that the discussion is going to emerge probably along the lines that, if we are talking about implementing a quality-systems

approach to GMP and product quality oversight, then I think the tendency is going to be that we are going to have to have additional data going into that to understand that a quality-system approach is in place.

So now you are sort of moving into this other conversation about assurance. It really doesn't have much to do with the CTD except if we make some changes in terms of taking on the pharmaceutical development and what the different requirements are in the various regions. That, of course, will impact, potentially, the CTD down the road. So it could be that there will be other additional requirements. There will be other ICH topics that may have to be reopened and looked at.

So things will be potentially revisited. Will this lead to some additional requirements? Perhaps, but I think a part of it is a little bit of a balancing act. If we are looking more in terms of information transfer and what we see, a lot of that reassurance that is going to come front-end versus what we do on the inspection side and how the two relate together, all of that has to be worked out.

I don't think anybody can predict right

now what that is going to do overall to whatever requirements, whatever guidelines, et cetera, may well be in place. We would all just be speculating at that point.

In terms of the narrow scope of the question and what is in the CTD, I think that part has been answered very accurately and correctly. Then you segue into things that are somewhat unknown at this point that have a lot to do with pharmaceutical development, with what additional things might be required in support of a GMP drug-product-quality approach that really is more of a quality-systems, risk-management, risk-assessment type of approach.

That is sort of the long answer, but you are right on target with where the thinking is tending to evolve. Of course, comments are very welcome in that area.

MR. MILLER: Loren Miller, PPD. I was interested in one slide that was presented where it was stated that the Common Technical Document was not considered a global dossier. I am not so sure industry didn't expect that, though, at the beginning when all this started out, that potentially a global dossier was possible.

In fact, I remember when all this started that, in fact, many people in regulatory affairs had that expectation. I seems to me, though, that with all the different modules and all the add-ons required by different countries, and a good example is the ISE-ISS controversy within FDA relative to what the document outlines now.

If you have ever had to write up one of these things and then you have to write it up two or three different ways for different countries, it is complicated. It is about as complicated as filing independent applications. So I think industry is hopeful that there would be some advantage on the harmonization side so that wouldn't need to be done.

MS. SHOWALTER: I am not sure there really is a response to that, but the only thing that I would say is that when the initiative was undertaken, I think that the regulatory authorities realized the challenges that would be involved, and that is why we did spend a number of years in the feasibility phase because it is a little more complicated than to just say it is strictly a format because we also understood that the way that the format got constructed has an impact on the

content as well and the way that the application is separated and reviewed within a regulatory authority, et cetera.

So I think we do understand that it is more complicated than that. I think we also understand the goal, ultimately, might be to have something that is more akin to a global dossier. But we have got to start somewhere. All the comments that I have heard, basically, are that this is a pretty good starting point.

With a little ability to undertake those challenges, you can, at least, submit a package that works in each of the regions. Part of the feasibility study at the beginning was that we knew companies were already doing this as well. There have been some test cases where they didn't say they were doing that, but, at various DIA meetings and so forth, companies would get up and report on the fact that they had achieved success already in doing this.

So I think all we can say right now is that it is a reasonable starting point. It is a good thing, conceivably, for the industry, also for the regulatory authority, to have some sort of standard format to look at. It kind of takes you

into the next wave of doing templates for reviewers and things where I think everybody agrees there is a lot more consistency.

So it is an evolving art form, I think it is fair to say.

Thank you, Tim. In order to get us back on schedule a little bit for some of the people who are here from the outside, I think what I would like to do, Justina, with your permission, is move the QT prolongation to the end so we could pick up, after Helle Gawrylewski's presentation, with the pharmacovigilance section.

The meeting allows the opportunity for outside speakers. We did have a request for an outside talk. This will be provided by a representative of a DIA committee that looks at the work that is being done on the CTD. I will let them introduce themselves and provide the presentation.

Presentation

MS. GAWRYLEWSKI: Good morning. My name is Helle Gawrylewski. I am Co-Chairman of the Drug Information Association's Medical Writing Special Interest Community, SIAC, Standards Subcommittee. With me is Barbara Kamm and also Sandy Heckler.

Barbara is Medical Writing Projects Manager at Allogen, but our comments do not reflect any official opinion of our respective companies or affiliates.

We are here on behalf of the DIA Medical Writing SIAC Standards Subcommittee and our basing these comments on several surveys, a roundtable discussion and several other team meetings within our group. We discovered that there are some misunderstandings about the ICH E3 Guidance on the format and content of clinical-study reports. So we recommend that the ICH Steering Committee consider reopening the guidance for some clarification and refinement.

Since its inception in 1990, various ICH working groups have successfully harmonized over 50 guidances that have measurably instituted time-saving and cost-saving effects on drug development.

The ICH E3 Guidance was one of the first major efforts to harmonize the very building block of a drug submission or marketing application in U.S., Europe and Japan. This particular working group should be commended for completing this difficult task because the spirit of global

harmonization is a commitment we see widely supported today but that was not the case at the time this guidance was developed.

We are not requesting major changes or revisions but recent developments motivate the request for refinements. Specifically good-guidance practices are in place now and we request that the E3 guidance be evaluated for consistency and clarity and also because of the eCTD standards that DTT and the study report tagging system proposed by the FDA has caused some confusion, although I have not seen the details specifically on the website, we have heard some of the details.

So, in our surveys and questioning, we found that the writers in the pharmaceutical industry, whether working for large or small PhRMA or independent for CROs can interpret the guidance section numbering in two very different ways. Some consider the numbering to be a template to be followed exactly while others consider the numbering system to be simply that of the guidance and not applicable to the CSR, which is the clinical study report.

Internal QA auditors are also interpreting

the guidance numbering and section content literally and they interpret it almost carrying to weight of law even though the level of flexibility is clearly discussed in the introduction of the E3. The message really isn't getting through.

Thus, we recommend a clarifying statement be issued about the extent to which these numbers should be followed and we recommend flexibility in the numbering scheme as long as the elements are present.

According to the ECD-CTD study report granularity document, apparently the appendix numbers are recommended to be exactly the numbers used in the E3 guidance as file names; for example, 16.1, 16.1.1 and 16.1.2. We recommend a simpler system of sequential numbering, 1, 2, 3, 4, 5, 6. There is really no need to consider the appendices as part of the report document. The separate granules that are recommended now are the synopsis, the report body and we are also recommending a separate granule for the study-supporting documents, the summary tables and the listing because these are generated by SAS. Then each appendix has a separate file, a separate tagging file after that.

Also some optional appendices should be allowed for unforeseen special reports. I know that the numbering, once it becomes specified in the eCTD, will be unchangeable so we are concerned about that being the case.

Other issues to address with the E3 guidance is the need to include some explanatory information about the contents of the recommended appendices and the inclusion of a location for data not mentioned specifically in the guidance at this time; for example, pharmacoeconomics, health outcomes and pharmacogenetics and genomics. These are new and increasingly included as endpoints in studies, yet they do not have a specific location in the CSRs.

Some types of information are mentioned in several sections and this could lead to some duplication, so we would recommend, for example, that statistical methods and statistical issues be placed together in a single section. Right now, they are spread in multiple sections.

For signatures and approvals, it should be possible to incorporate the sponsor's medical officer signature in a report appendix and hyperlink to signatures required regionally in

Module 1 or place all signatures in Module 1 with just a placeholder in CRSs. More clarity on this issue and in the CTD recommendations would be welcome.

the final point is that if essential documents are maintained in the trial masterfile according to GCP recommendations and are available at all times for reference if requested, what would be the streamlined list of documents essential for review and interpretation of study data.

For example, one appendix requires documentation of interlaboratory standardization methods and quality-assurance procedures. Some companies have interpreted this to mean inclusion of all laboratory manuals for routine laboratory tests.

For accredited laboratories, this represents an extra cost in resources, both human and paper, in scanning the voluminous documents that this would entail, documents that a reviewer might not need and might not even want. So, in an effort to supply what the reviewers do need and to avoid the extra costs in time for industry, could more explanatory texts be added to the required appendices and some appendices actually deleted

altogether if the data have not proven useful.

This would be an ideal time to review that because, once these eCTD specifications go into effect, these appendices are there forever and if there is unclarity about the content of these appendices, it will lead to some difficulties later on.

According to Commissioner McClellan's recent statements at the DIA conference, we need to perform efficient global risk management, provide clear guidances and use the best science available for creating a standard set of rules to reach our policy goals in the least burdensome way. Large PhRMA has had the experience to use this least-burdensome approach but smaller companies are struggling.

So the details of some minor issues that might add to the clarity of this valuable document will be provided for the record as a starting point for consideration. I have some details but I don't want to read all of that into the record now.

In conclusion, our recommendations for reevaluation of the ICH E3 guidance include the structure and numbering of sections, specific guidance on the contents of the key appendices,

duplication of information in more than one section, eliminating that and adding some missing locations for other types of information, and clarity on signatures and placement options for signatures.

A Q&A area on the ICH website with harmonized responses and clarifications similar to the CTD Q&A area would work well for some of the more minor areas.

Respectfully, Helle Gawrylewski and Barbara Kamm. Thanks very much for listening.

MS. SHOWALTER: Thank you.

We are quite a ways behind schedule, I understand. If we could do a little bit of a shifting of the agenda and take up the pharmacovigilance topics next. The first speaker under that section would be to talk about MedDRA MSSO and then we will proceed with E2D after that, E2E, and then we will come back to E14, a Q-T prolongation topic.

Pharmacovigilance

MedDRA

MR. REVELLE: First I would like to thank the FDA for inviting us here to speak. It is a good opportunity, I think, for us to at least give

a little update on MedDRA and about some of the activities that we are going forward with.

I will give a little bit of an intro about MedDRA so you will get a sense of what I am talking about but I think MedDRA actually represents a ICH success story. It has come through the whole ICH process out of the M1 Expert Working Group and is now actually in wide use in the pharmaceutical industry. I will talk a little more about some of the other related sort of issues.

So what are the objectives of MedDRA? It is to provide an international multilingual medical terminology really to be used across the full spectrum, from clinical-trial drug development through postmarket reporting. The real goal, I think, or one of the several goals is to have standardized communication not only just from industry to regulators but between industry, themselves. They have actually found it to be very useful tool, especially during this consolidation period within industry, itself.

MedDRA has a pretty wide scope and it is fairly different than some of the terminologies that we are replacing. It goes, obviously, across adverse events, but medical history, physician

examinations, medical and surgical procedures, laboratory tests, just to give you the sense of the spectrum.

In fact, I think this next slide is the listing of all of the top-level what we call system-organ classes in MedDRA to give a sense of the scope of the areas covered within the medical terminology.

I work for an organization called the MedDRA Maintenance and Support Services Organization which is really tasked to do a couple of different things, the first of which is to maintain and continue the development of MedDRA through an international change-request process. So, as you subscribe to MedDRA, you have the rights to be able to submit change requests and then you receive MedDRA on a twice-a-year basis at this point.

Our other goal is, obviously, to foster MedDRA use worldwide through communication, education and some services that we provide.

That is a very quick introduction to MedDRA and, hopefully, it filled in a little bit of gaps for you if you have those. I am going to talk about a couple of different issues that are

significant, at least in the MedDRA world right now. We started a process called a MedDRA blue-ribbon panel. As you may be aware, MedDRA, or the MSSO, started the maintenance of MedDRA in November of 1998.

Initially, the process of maintenance was relatively simple because, while MedDRA was very well-developed by the time we got it, there were still some areas that needed some work. So, to fill those holes, at that point in time, was relatively simple.

More recently, the task of maintenance has been more complex and the number and the types of changes that we are getting are much more granular and much more fine in their distinction between existing terms. We are also trying to balance between the development and the growth of the terminology versus the value of that growth to the subscribers and users of the terminology.

So, as a part of that, we are trying to implore the users to provide more rationale for changes so we don't just automatically include every change that we receive.

To aid in this process, we have worked with our management board which consists of both

regulators and industry to come up with this concept of the blue-ribbon panel to give us additional input for guidance and policy regarding the types of changes we should consider and continue to consider for MedDRA.

So we talked about things regarding the general scope and specificity of MedDRA as well as to support the consistency of maintenance activities. Quite honestly, our biggest concern is to make sure that we are consistent in what we include or exclude through the life of the maintenance of MedDRA.

The panelists reflected the makeup of the ICH so we had regulators as a part of the panel as well as industry representatives. We also included our subscribers as observers and, actually, they are really participants in the panel through questions and answers.

The end result of this panel is for them to develop with really our assistance a series of recommendations that will provide to our management board before we will make them public, but the idea is, again, to refocus the efforts of the MSSO to make sure it is consistent with what the user community is looking for. After we get our

management board approval about those recommendations, we will publish them on the MSSO website and, obviously, make it available to all of the users of MedDRA.

We thought it was a great success, actually, for us to hold this blue-ribbon panel. We thought the format worked very well. So, as a result, we actually plan on continuing to have these blue-ribbon panels on other MedDRA-related topics and right now we are talking about about two per year.

Another sort of an interest area in MedDRA is MedDRA is not only available, obviously, in English but part of our task is to maintain it in multiple languages. From the outset, MedDRA, from its earliest version that was delivered, Version 2.1, was available in English and in Japanese.

Through the series of different releases, there have been other languages added including Spanish through the lowest level term level, which is the lowest level of detail in MedDRA. Other languages, like French, German, Portuguese have been translated but only through the preferred term level of MedDRA which is the next level up of detail, the lowest-level term, which I will get

into, is somewhat problematic for some of the languages. Dutch is scheduled for release in September of 2003.

One of the true values that we saw in even the developers of MedDRA and the M1 Expert Working Group saw was that each MedDRA term is assigned a unique MedDRA code so there is a possibility that you could code in one particular language and output in another based on the linkages of those codes. That works today. I will talk about some issues related to the translations next.

Typically what it revolves around is the lowest-level term which tends to have some synonyms, some colloquial terms especially in English. I make an example here of edema, edema spelled both ways. MedDRA incorporates the English version, both the North American version of English that I speak as well as the British English that is spoken across the way.

Obviously, that poses a question when you are performing translations, is how do you translate that to Spanish. How do you translate that to Japanese? Right now, unfortunately, some of the languages are handling that differently. So we are considering that as a potential next topic

for a blue-ribbon panel because it could destroy some of the utility if we don't maintain a reasonable link of the translations between the different languages.

One of the other major topics that we are working on is some efforts to coordinate our MedDRA maintenance with a CIOMS group that, interestingly enough, had independently come to the same conclusion that we had which MedDRA had gotten a wide acceptance and wide implementation for the codification of clinical-trial data or just clinical data in general.

But, to extract data once it has been coded in MedDRA was starting to become somewhat of a more difficult task. So both the CIOMS group and the MSSO initiated two separate activities to try to address this. The CIOMS group started to develop a product called the standardized search queries and the MSSO was developing something called MedDRA Analytical Groupings.

We started to notice that both of us were working on the same thing and thought it might be better if we combined our efforts. So what we have done is we now are working together on a single working group to develop what are--of course, we

had to come with a new acronym, our standardized MedDRA queries.

During that process, we have held a series of different meetings to try to coordinate our efforts. They have developed a series of different SSQs. We developed a series of MAGs. We want to consolidate that effort.

To give you a little bit more sense of what I might be talking about is an SMQ is a group of MedDRA terms that relate to a defined medical condition or area of interest. So it combines, say, the laboratory test, the diagnostic, the signs and symptoms all related to a very specific issue that you might be looking for.

Then you could use that as kind of a stored query to go against your data to try to pull the cases of interest and make it a little more useful for you.

Just to give you a sense of where we are going, you will see what are generally considered to be very interesting topics especially from the safety side, to be able to develop what are the terms in MedDRA that are relevant to these particular SMQs and then define that, distribute that to the users of MedDRA so they can start using

that as a tool against their own database.

They could also use it as a tool for communication against their own database. They could also use it as a tool for communication amongst themselves and we think eventually to regulators as well. I might make a note that a regulator is including the FDA, EMEA and others, who are all involved in the development of these SMQs and are very much interested in the outcome and the eventual product coming to fruition.

You might notice that there are four of the SMQs that are asterisked. They will be coming out in the next version of MedDRA which is scheduled for release in September of this year.

I will give you a little bit more of our plans for the SMQs. It is a two-year collaborative process that we have in mind right now with the CIOMS group. Obviously, MedDRA or the MSSO would continue to maintain these SMQs after that point, but at least this intensive effort with CIOMS would continue for the next two years.

IFPMA would own the rights to these SMQs as they do with the rest of MedDRA. The MSSO will maintain and distribute with each MedDRA release so, as things change in MedDRA, we will either add

new terms to an SMQ or, potentially, remove them. It is part of a standard MedDRA subscription so there is no additional cost associated with.

Obviously, we need to develop additional documentation to make sure users of MedDRA will have some sense about what we are talking about.

I mentioned before that the first set of SMQs will be scheduled for release this September. It will be part of the MSSOs change-request process so that the subscribers to MedDRA could also either identify additional SMQs to be developed or recommend changes for existing SMQs.

With that, I will take any questions you have regarding MedDRA.

MS. SHOWALTER: Thank you. Questions?

MS. GAWRYLEWSKI: I have one quick question. Being part of industry, there is a heavy mention of industry involvement and regulator involvement. I am just assuming, and this is probably a really naive, stupid question, that practicing physicians in the private sector are also involved in developing this. It is not really mentioned very often or well-known. How are they involved, actually practicing physicians.

MR. REVELLE: MedDRA is actually available

through the GPRD which, I think, is a U.K.-based group that is trying to make terminologies available to regular practicing physicians. So we are looking at other groups to try to get MedDRA down to that level as well so they are not excluded from the process.

The initial development, obviously, was for the pharmaceutical and biotechnology industry. But it is, I think, within our scope or at least in our intent to try to serve them as well.

MS. SHOWALTER: Thank you.

Now we will move on to the next talk which is Susan Lu is going to bring us up to date on E2D. That would be post-approval safety-data management.

E2D: Post Approval Safety Data Management

MS. LU: ICH E2D is a guideline of post-approval safety-data management and provides standard definitions and terms for key aspects of expedited reporting. This guidance is intended to help harmonize methods for gathering and evaluating safety data.

This topic was adopted by ICH in February, 2002 and the working group has met previously three times since June of 2002. The former name for this guideline was V2, the second of three

pharmacovigilance topics but, at the February meeting, the ICH Steering Committee renamed it E2D. The current status E2D is Step 1; that is, building consensus through discussions between regulators and industry for harmonization of concepts in postmarketing safety.

E2D is an expansion of an existing E2A guidance which set standards for clinical-safety data management. E2D is similar in style and content to E2A and considers how those concepts can be applied to the postapproval phase. Relevant concepts and recommendations from the CIOMS-5 report on pharmacovigilance would be incorporated into this guideline.

The title of the first three sections of the guideline are identical to those in E2A. There is a short introduction, a section on definitions and terminology associated with postapproval drug-safety experience and standards for expedited reporting.

A fourth section on good case-management practice is a topic originating from CIOMS-5. The introduction section states the purpose of the guideline which is to establish an internationally standardized procedure in order to improve the

quality of postapproval safety information, to harmonize the way to gather and report information. This guideline is based on concepts from E2A and although E2A standards and definitions have been applied by regulators and industry, there is a need to formalize this. Also, there is a need for definitions that are specific to the postapproval phase.

The second section of the guideline is the definitions and terminology for postapproval drug-safety experience. This includes basic terminology, formally defined in E2A such as an adverse event, an adverse drug reaction. The criteria for seriousness and expectedness is also discussed. There are also new definitions that are not in E2A such as labelness, which refers to local product labeling, and listedness, which refers to the core-company datasheet.

Class ADRs is also addressed in the premise that these are not automatically considered expected unless the labeling describes an event as occurring specifically with the product.

Other definitions such as healthcare professionals and consumers, we really don't address these in U.S. regs but the working group

felt that these are important to include because, outside of the U.S., these reports are not considered valid unless there is confirmation by a healthcare professional.

There is also an extensive section within the definitions and terminology that describes the sources of individual case reports. Most of these are described in the CIOMS-5 report.

The third section of the guidance is standards for expedited reporting which addresses what should be reported. It states that single cases of serious unexpected adverse events is always subjected to expedited reporting. It also does describe some other cases such as lack of effect. These are generally not subject to expediting reporting except in certain circumstances where there is an exacerbation of disease or the product is used in the treatment of life-threatening disease.

Drug-dependence type reports are also addressed and these are events that may qualify for expedited reporting of not associated with further adverse events unless it is described in the product labeling. In contrast, reports of overdose with no associated adverse outcome should not be

reported as adverse drug reactions.

Reporting time frames are also addressed in this section. The minimum criteria for reporting is the minimum dataset that consists of an identifiable patient, an identifiable reporter, a suspect product and an adverse event. The time clock start point is defined as the date when a company first receives a report that fulfills the minimum criteria for reporting.

The last section of the guideline is good case-management practices which stresses the need for accurate and complete information to identify and assess adverse drug-reaction reports. The five topics in this section are assessing patient and reporter identifiability, the role of narratives, single case evaluation, follow-up information and how to report.

Assessing patient and reporter identifiability is important to verify the existence of a real patient reported. Identifiers would include patients initials, code, sex, age, category, name and phone number of the reporter. Establishing identifiability minimizes case duplication and this facilitates a follow-up of individual cases.

The role of narrative sections states that a narrative of a case report should summarize all the relevant clinical information including the patient characteristics, therapy details, medical history, clinical course of the event including outcome, laboratory data and any other information that would support or refute the evidence or diagnosis for an adverse drug reaction.

It also states that an autopsy should be provided when available and ICH E2B establishes that company narratives are required for all reports of serious reactions.

The single case evaluation section proposes review for correct interpretation of medical information and for quality and completeness of information. This also emphasizes the need for sound clinical review.

The follow-up section stipulates that the highest priority for follow up is for cases of serious unexpected events. The use of a focused line of questioning such as a questionnaire is encouraged to capture clinically relevant and important information and follow up is suggested to be performed by healthcare professionals with pharmacovigilance training.

Our goal in this working group is to ensure that the contents and concepts are consistent with current-use regs and guidances and with the safety-reporting proposed rule. As I mentioned earlier, the working group is in Step 1 which is consensus building and there may be further changes. There are still issues, particularly in the definitions and terminology section and, to a lesser extent, in the expedited reporting section which will require further discussion.

Looking ahead, there may be additional topics to consider for incorporation into E2D. Some examples of these would include issues such as medication errors, the concept of requiring full datasets for all serious adverse drug reactions, always expedited reports and requiring full documentation for reports of death and hospitalization.

Any questions? Thanks.

MS. SHOWALTER: Thank you, Susan.

The next-to-last topic that we have is E2E, pharmacovigilance planning. Paul Seligman is going to do that topic for us--if he is here he will, anyway. But if he is not here, and he

doesn't seem to be at the moment, Justina why don't you do QT prolongation and then we will come back to that one.

E14-Clinical Part of QT Prolongation

MS. MOLZON: I need to start this presentation with a disclaimer. I am here pinch-hitting for Dr. Douglas Throckmorton, the Division Director for Cardiorenal. He is actually the rapporteur for this group and this group is the newest expert working group, so we thought it would be a good idea just to fill you in on what has been going on and the plans for Brussels.

The point of this whole topic which deals with the clinical evaluation of QT-interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs is that that is a concern about drug-induced proarrhythmias. The goal of the documents that are being discussed in this expert working group is to provide recommendations to drug developers concerning the design, conduct and interpretation of clinical studies to assess the potential for delaying cardiac repolarization.

Currently, in ICH, we have a pharm-tox or safety topic called S7B which looks at the safety pharmacology studies for assessing the potential

for delayed ventricular repolarization or QT-interval prolongation by human pharmaceuticals. So this is the pharm-tox or non-clinical aspect of the clinical document that is under way.

This safety document was released for consultation under Step 2 of the ICH process in February of 2002. It was published in the Federal Register. Notice of its being released for consultation was in the Federal Register in June of 2002. Then we sort of held it at this point because we were waiting for the clinical document to develop so the two can proceed at the same time.

So the safety pharmacology people are actually gathering information to help feed into the clinical document.

Now, there is some additional background to this ICH topic. It started with a document that was drafted by Canada's Therapeutic Products Directorate. I believe that this was in response to a coroner's inquiry into some of the products that were causing QT prolongation which resulted in several deaths in Canada.

CDER was working on a similar document because we had similar concerns and we recognized the value of a joint effort and, further, the

effort of a harmonized ICH document. So we talked about introducing this topic into the ICH process which is unusual because, generally, industry proposes topics. But here this was a regulatory concern and the regulators wanted to introduce the topic. But the regulators recognized the need for expertise outside of the ICH process.

Just to talk about some time lines; Health Canada came out with a draft guidance document on QT-interval prolongation in March of 2001. That document was combined with FDA efforts and a proposed concept paper was put together in November of 2002.

We then developed a consultation workshop held here in Washington, D.C. in January of 2003. What we were trying to do with this consultation process was to sort of jump-start the ICH process by using a draft or final document that was being developed in one of the ICH regions that would provide a strong foundation for the development of an ICH guideline.

So, instead of having a very brief concept paper being introduced into the ICH process, you have a fairly well-developed document to start the ICH process. This more developed document would

ensure the inclusion of the necessary experts outside of the ICH process. So the idea here was to involve the people with necessary expertise that would not be necessarily part of the ICH working group.

So, to develop or to enable inclusion of this specific medical expertise, the preliminary concept paper that the FDA and Canada's Therapeutic Products Directorate worked on was posted in the DIA, the ICH, the TPD and CDER websites on the same day, November 20 of 2002. This was so that everybody that was interested in the document could read it before we had discussions in a DIA meeting where we invited experts outside of the ICH process for a very scientific discussion.

So we worked with the North American Society of Pacing and Electrophysiology to make sure the correct expertise was included in this discussion process. And the ICH working group for S7B plus this newly established group on QT prolongation was present for the discussion so they could listen to the scientific discussion and then take those thoughts back into the ICH process.

This was a bit of a different approach for all of us because it is outside the norm for the

regular guideline development within ICH, CDER and TPD. It was also a different venue and process for the Drug Information Association because this was very academic setting to provoke academic discussion. This was a meeting that took place at the University of Maryland at Shady Grove, so it wasn't a hotel. It was just an academic huge conference room.

More than twice the number of panelists were on the program. We must have had twenty to thirty panelists so that we had a wide variety of expertise from a wide variety of settings; academia, hospitals, clinics, CROs, et cetera. It ended up being one of the largest programs outside of the Annual Meeting for DIA, with over 620 people attending.

To capture all of the effort at this workshop, there was a transcript to capture the discussion and the resulting recommendations and conclusions were incorporated into the document that had been posted for consideration. The recommendations and conclusions from the workshop were incorporated into the document for ICH consideration.

This document was fed into the ICH QT

Prolongation Working Group during the meetings in Tokyo this past February. The result is, hopefully, going to be a harmonized approach to QT prolongation.

Now, the following slides are from Dr. Doug Throckmorton and they represent his report to the ICH Steering Committee at the meetings in Chiba, Japan in February of 2002. Basically, he just provided an outline of the guideline. The guideline, I believe, has seven sections; background and scope, clinical-trial design--that includes Phase I through evaluation, Phase II and III evaluation. Section 3 is a collection and analysis of QT-interval data. Section 4, analysis of QT interval and ECG wave-form data. Section 5, adverse-experience collection. Section 6, regulatory implications, labeling and risk management. So I mis-spoke. There are only six sections.

Dr. Throckmorton talked about progress of the working group at those meetings in Japan. There was an initial discussion and revision of the document, so this is the document that came out of the workshop that was put on before the ICH meeting.

There was an identification of items requiring additional data or discussions such as operating characteristics of nonclinical assay systems. So this is where the S7B group fits in, and the potential use of nonclinical data to inform design of a thorough clinical QT study.

So, how can you use the nonclinical, preclinical or animal data to support what needs to be done or not be done in the clinical studies. Trial-design issues were also discussed and this included validation of Phase I study assay sensitivity, use of data from thorough Phase I assessment and to inform Phase II and III trials.

The action items that were presented to the steering committee was there was, believe it or not, a huge controversy about what to call this topic. Logistically, it should have been E13 but, for some reason, in this very scientific forum, that was not acceptable. So it is now E14 skipping E13.

Also the working group edited the version of the concept paper for presentation by the steering committee and they discussed the clinical research necessary to parallel the S7B research initiative. There was the possibility of an

interim meeting or teleconference following the availability of nonclinical data from the S7B working group.

I don't believe that actually took place because it wasn't necessary, but it had been proposed.

Las month, in CDER, the Cardiovascular and Renal Drugs Advisory Committee held a two-day meeting on nonclinical studies and their sensitivity and specificity. The potential impact of nonclinical testing on the design of the thorough clinical QT evaluation will be discussed in Brussels. So we are also using some of the information from this recent advisory committee to feed into the Brussels discussion.

The goal in Brussels is to reach a Step 2, so that would be a document that would be put out for comment. So, once again, the document will be available for anyone to comment on and I believe that this is a very short turnaround for an ICH document. So, by jumpstarting the ICH process and putting a lot of expertise or whatever into the document initially, you can actually speed up the ICH process.

I think that is it. Any questions should

go to Dr. Throckmorton but I would be pleased to pass them on. Does anyone have any questions?

MR. PARKER: Ford Parker from Hoffman LaRoche. One thing we were surprised to see in the document was, at the DIA meeting, people were very opposed, including people that do a lot of these ECG studies like Joel Morganroth that the document included requiring detecting a mean QTC change of 5 milliseconds, which he said was nearly impossible and our calculations, from the standard deviations that you typically see in healthy volunteers, is about 12 to 14 milliseconds for QTC, would require upwards of 100 subjects per arm.

In addition to that, you also recommend using moxifloxacin as a control which causes changes of 5 to 10 milliseconds which, supposedly, the agency thinks is inconsequential clinically. So the question is why would you expect people to detect 5 milliseconds in a 500-subject study where you don't believe these changes are even clinically meaningful.

MS. MOLZON: First of all, I don't know if that information is actually still in the document because, as I said, recommendations from the DIA workshop were used to revise the document that went

into the ICH process.

MR. PARKER: It was in the February 6 document after the DIA meeting. It was still there, 5 to 6 milliseconds.

MS. MOLZON: Okay. I am not the expert here. But I still don't know if that information was rediscussed in Chiba, Japan and is still in the document that will be posted at Step 2. So what you need to is, when that document is posted, if you have comments on that specific section, just make sure that you send them in to the docket for discussion at the next phase.

MR. PARKER: Okay. A second general question is can outside persons attend the Brussels meeting? Is this a closed meeting or is it open to the public.

MS. MOLZON: Your representative will be the PhRMA representatives on the committee. So, if you have concerns, you should work with your PhRMA representative. But it is a closed meeting. It is just open to the ICH partners, so it would be PhRMA--Christelle showed the chart of who is involved, so it will be PhRMA and FDA for the U.S., EFPIA and the EU for Europe and then JPMA and MHLW for Japan.

Your representative will be the PhRMA person on the committee. So, if you have concerns about this specific issue, you should get in touch with the PhRMA rep on the committee and then they can relay these concerns to the expert working group.

MS. SHOWALTER: Let me just further comment on that. You actually have the possibility of conferring with the PhRMA, which is the U.S. industry rep, but also with the EFPIA representative as well, which would be the European industry rep, so you would have more than a single opportunity to talk to your industry representation.

I think that the names of those representatives should be listed on the ICH website. I think we have a list of all of the experts for the various expert working groups. So you will see who that person is and you will be able to contact them that way.

Thank you, Justina.

Dr. Paul Seligman is with us now and he is going to provide the update on the other pharmacovigilance topic which is E2E, Pharmacovigilance Planning.

E2E: Pharmacovigilance Planning

MR. SELIGMAN: Good afternoon. The Pharmacovigilance Planning Group or E2E is one of the newest topics being considered by representatives at the ICH. The interest in and genesis of this topic comes primarily out of Japan's recent regulation requiring early postmarket pharmacovigilance, or EPPV, for newly marketed products in that country.

Dr. Yusuki Tanagawara from KO University who represents the Japanese Ministry of Health, Labor and Welfare is the co-lead of this new working group along with Dr. Peter Arlette from what was formerly known as the British Medicine's Control Agency.

Myself, along with Dr. Robert Ball and, most recently, Dr. Miles Braun from CBER have represented the FDA on this working group. The question basically before the E2E Working Group is that, beyond the current harmonized regulatory requirements for submitting reports of adverse drug events, should there be international agreement and a common understanding regarding additional surveillance data to be collected and/or studies to be conducted in the post-marketing period and, if

so, should the sponsor of the product submit a plan to be reviewed by regulatory authorities prior to the approval or licensing of the product that describes essentially these additional studies or additional surveillance; hence pharmacovigilance planning.

The basic premise of this planned pharmacovigilance approach is that it offers the opportunity to reduce risk and increase benefit of medicines to the public of marketed products. The scope of the guideline as it is currently outlined is essentially to provide guidance to industry in the preparation of a pharmacovigilance plan prior to the launch of a product.

It focuses primarily on new drugs, biologics, new formulations and any new indications. It is essentially meant to lay out a pharmacovigilance specification which essentially is the risk basis or safety basis for developing the plan. It describes the initial content or elements of such a plan and it also talks about the types of postapproval studies that may be utilized to examine a particular safety question postmarket.

This effort has many similarities to FDA's current effort to develop guidance on good

pharmacovigilance practice and postmarketing risk assessment. Some of you may be familiar with the public meeting we had last April 9, 10 and 11 here in Washington and the concept paper which is currently on the website which is serving as the basis for the draft guidance that will be provided by the FDA in the fall as part of our PDUFA-3 agreement.

As these two efforts more forward in tandem, the ICH thinking has been shared with the drafters of FDA guidance and vice versa, so we want to make sure that our guidance development is well harmonized with ICH. This ICH document, I think, is probably best described as in its earliest phases of development.

That is really all I have to say. I am happy to field any questions about E2E or what this pharmacovigilance planning group is up to.

MR. MILLER: Loren Miller, PPD. Is this guidance set up to establish a safety marketing plan prior to launch that is kind of sequential plan; that is, you are ready to evaluate safety in a very short period of time, let's say, after your product is launched. Are you required to collect data at earlier time points than you normally would

by current regulations? What is the thrust of it? Is it just a planning document, per se?

MR. SELIGMAN: Essentially, it is a planning document. In the PDUFA-3 agreement and the goals letter, they talk about more either intense or concerted surveillance for the first two to three years postmarketing. I think this pharmacovigilance planning essentially is going to parallel that although, in the ICH document, they have not gotten down to that sort of level of specificity yet.

I think it is primarily focused on that sort of early period of time following the introduction of new product.

Any other comments or questions? I feel like I have just zoomed in and zoomed out.

MS. SHOWALTER: There don't seem to be any. So, thank you.

MR. SELIGMAN: As I say, there are PhRMA representatives on the committee; Linda Hoselly and Janice Bush and Waiju Dai. They are the three who have served to represent PhRMA's interest in the early development of this paper.

MS. SHOWALTER: Thank you.

I want to adjourn the meeting. I thank

everyone for their participation and your indulgence with our bending the agenda a little bit to try to accommodate everybody. I know we have run long today but these meetings are very valuable to us and we will continue doing prior to each ICH meeting. So we really appreciate your participation.

We also always welcome outside speakers. We are very thankful that we had one today and we would hope to more of that in the future.

The transcript will be made available on the web. Again, I just want to thank everyone including our speakers for their time today. I know it is difficult getting ready for this meeting to take time out of the schedules, but, again, we think it is very valuable.

So thank you and we adjourn the meeting.

[Whereupon, at 12:50 p.m., the meeting was adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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